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(54) Title: EMULSIONS OF PARAMAGNETIC CONTRAST AGENTS FOR MAGNETIC RESONANCE IMAGING (MRI), CONTAINING AN ORGANIC CHELATOR HAVING AN UNSATURATED ALIPHATIC GROUP

(57) Abstract

Emulsions of paramagnetic contrast agents and processes of making and using them are disclosed. The emulsions contain water, a dispersed oil phase and a complex of a paramagnetic metal ion and an organic chelator having a C_{10}-C_{30} unsaturated aliphatic group. The emulsions are very stable and therapeutically acceptable for intravenous administration to enhance MRI.

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EMULSION OF PARAMAGNETIC CONTRAST AGENTS FOR MAGNETIC RESONANCE IMAGING (MRI), CONTAINING AN ORGANIC CHELATOR HAVING AN UNSATURATED ALIPHATIC GROUP

TECHNICAL FIELD OF THE INVENTION

This invention relates to emulsions of paramagnetic contrast agents, and processes of making and using them. More particularly, this invention relates to novel emulsions that contain water, a dispersed oil phase and a complex of a paramagnetic metal ion and an organic chelator having a C_{10}-C_{30} unsaturated aliphatic group. The emulsions are very stable and are therapeutically acceptable for intravenous administration to enhance MRI imaging.

BACKGROUND OF THE INVENTION

Magnetic resonance imaging (MRI) has been developed in recent years and, for improved imaging, paramagnetic contrast agents have been given to patients prior to imaging. A number of patents disclose paramagnetic MRI contrast agents including, for example, U.S. Patents 4,647,447; 4,859,451; 4,957,939; 4,963,344; 5,021,216; 5,064,636 and 5,120,527; and PCT application WO 92/21017. These patents are considered to be illustrative of prior references in the field and are not intended to be the most pertinent references.

Paramagnetic agents of the type disclosed in the above patents have been administered to the patient in the form of aqueous solutions. In addition, paramagnetic oil emulsions have been provided for MRI imaging in the gastro-intestinal tract as disclosed in U.S. Patents 5,064,636 and 5,120,527. There has been a continuing effort to develop complexes of paramagnetic metal ions as MRI contrast agents that function effectively as organ imaging agents as well as blood pool agents, or for other uses, such as agents for imaging the bone marrow, spleen, liver or lymph nodes. Liposomes have also been studied as MRI contrast agents, and, more recently, as disclosed in PCT application WO 92/2107, lipo soluble contrast agents may be administered in the form of lipid emulsions. The contrast agents of the PCT application are useful in the imaging of the liver, blood pool and reticuloendothelial system (RES).

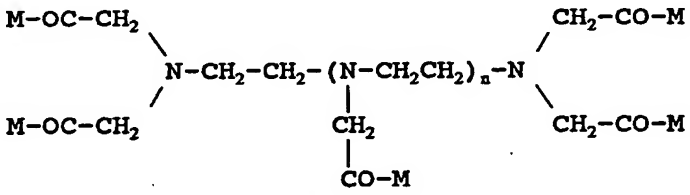
Notwithstanding the prior efforts in the field, there is a continuing need for improved MRI contrast agents. In particular, MRI contrast agents are needed which function effectively as organ imaging agents as well as blood pool agents, and for general imaging of the reticuloendothelial system. Stable and versatile MRI contrast agents are needed, especially for intravenous use.

SUMMARY OF THE INVENTION

This invention is directed to a physiologically acceptable emulsion for enhancement of MRI imaging

comprising water, a dispersed oil phase and a paramagnetic metal chelate complex having a C_{10}-C_{30} unsaturated aliphatic group. It has been discovered that very fine and stable emulsions may be made using such chelate complexes. These emulsions remain stable after heat sterilization. Moreover, these emulsions may be used intravenously and provide excellent MRI images.

More particularly, the physiologically acceptable emulsion for enhancement of MRI imaging comprises water, a dispersed oil phase and a complex of a paramagnetic metal ion and an organic chelator having the formula



wherein from 2 to 5 M groups are hydroxyl, n=0 to 2, and any remaining M group is NR_1R_2, each R_1 is a C_{10}-C_{30} unsaturated aliphatic group and R_2 is hydrogen, hydroxyl or a C_1-C_2 alkyl.

The metal ion is a lanthanide element of atomic numbers 58-70 or a transition metal of atomic numbers 21-29, 42 or 44, most prefereably selected from a group consisting of Gd(III), Mn(II), iron and dysprosium. The organic chelator is preferably an acid selected from the group consisting of ethylenediaminetetraacetic acid and diethylenetriaminepentaacetic acid. Mono- or bis(amides)

having an unsaturated C_{14}-C_{22} group are physiologically preferred. It has been established that the unsaturated group may have one, two, three or more double bond(s) at a number of different locations in the group, and very fine, stable emulsions are still achieved.

The MRI emulsions for intravenous administration have an average particle size less than about 1 micron, preferably on the order of about 0.2 to about 0.4 micron. In other embodiments, the emulsions comprise water, a dispersed oil phase selected from the group consisting of an oil and a fluorochemical, and mixtures thereof, a surfactant, and a dispersed complex of a paramagnetic metal ion and an organic chelator. The emulsified particles of an oil and/or a fluorochemical ("PFC") in water are hereinafter sometimes referred to as the "dispersed oil phase". The paramagnetic agent may be effectively suspended or dispersed in the stabilized emulsion for delivery to an animal or human subject.

In contrast to prior MRI agents and compositions, the MRI emulsions of this invention are very stable and exhibit excellent storage stability at room temperature or other ambient conditions. Furthermore, the inventive emulsions produce excellent MRI images of organs, blood pool and the RES.

This invention also includes methods of making emulsions containing paramagnetic agents. Other objectives of this invention and advantages will become apparent from the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

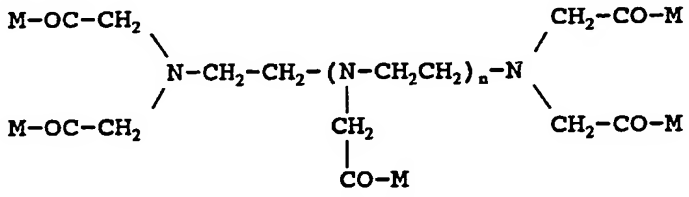
The MRI emulsions of this invention comprise an oil and/or a fluorochemical (PFC) emulsified in water and contain a paramagnetic metal chelate complex. In certain cases, the chelate complex may act as a surfactant and, thus, additional cosurfactant may not be needed. In most cases, a surfactant is added. In general, the oil and/or PFC may be contained in amounts from about 0.5 to 50% by weight. More specifically, for instance, in medical applications for intravenous (IV) MRI contrast agent delivery, the preferred amounts of PFC and/or oil with surfactant are minimum amounts to effectively disperse the agent in a stable emulsion. For oral, rectal, or other delivery, far greater amounts may be desirable. For IV use, about 25 w/v% is a practical limit for the oil, or about 55 v/v% for the PFC, because of viscosity limitations for an intravenous product. Preferred ranges are about 5 to 20 w/v% for the oil or about 5 to 50 v/v% for the PFC. Emulsions exhibit high viscosity (or a gel-like consistency) at higher oil or PFC levels. The surfactant may be contained in amounts from about 0.5 to about 10% by weight, usually about 1-5% by weight of the emulsion. Generally, the MRI agent may be dispersed in varying amounts up to about 30% by weight, depending upon dose, efficacy and safety requirements. Thus, an IV emulsion may preferably contain a lesser amount of MRI agent up to about 10% by weight. For instance, in oral or rectal administration, an MRI imaging agent such as a

gadolinium salt of a bis(oleylamide) of diethylenetriaminepentaacetic acid may be used as high as about 50% or more. If desired, the emulsions may be diluted with isotonic saline, or other agents, to produce lower concentrations. These components are identified with greater particularity as follows.

A. Paramagnetic Metal Chelate Complex

In a broad form, this invention is directed to a physiologically acceptable emulsion for enhancement of MRI imaging comprising water, a dispersed oil phase and a paramagnetic metal chelate complex having a C_{10}-C_{30} unsaturated aliphatic group. It has been discovered that very fine and stable emulsions may be made using such chelate complexes. Moreover, these emulsions may be used intravenously and provide excellent MRI images.

More particularly, the physiologically acceptable emulsion for enhancement of MRI imaging comprises water, a dispersed oil phase and a complex of a paramagnetic metal ion and an organic chelator having the formula



wherein from 2 to 5 M groups are hydroxyl, n=0 to 2, and any remaining M group is NR_1R_2, each R_1 is a C_{10}-C_{30}

unsaturated aliphatic group and R_2 is hydrogen, hydroxyl or a C_1-C_2 alkyl.

The metal ion is a lanthanide element of atomic numbers 58-70 or a transition metal of atomic numbers 21-29, 42 or 44, most preferably selected from a group consisting Gd(III), Mn(II), iron and dysprosium. The organic chelator is preferably an acid selected from the group consisting of ethylenediaminetetraacetic acid and diethylenetriaminepentaacetic acid. Monoamides or bisamides of an organic acid selected from a group consisting of diethylenetriaminepentaacetic acid and ethylenediaminetetraacetic acid are used wherein each R_1 is a C_{14}-C_{22} group selected from the group of oleyl, farnesyl, geranyl, erucyl, elaidyl, linoleyl, ricinoleyl, petroselinyl, linolenyl, vaccenyl, linderyl, palmitoleyl, palmitelaidyl, myristoleyl, and myristelaidyl. The N-methyl, N-ethyl, and N-OH (where R_2 = methyl, ethyl, or OH for each R_1) derivatives of these amides can also be included as examples.

Specific examples of chelate complexes include gadolinium diethylenetriaminepentaacetic acid bis(oleylamide), gadolinium diethylenetriaminepentaacetic acid mono(oleylamide), gadolinium diethylenetriaminepentaacetic acid bis(farnesylamide), gadolinium diethylenetriaminepentaacetic acid bis(geranylamide), gadolinium diethylenetriaminepentaacetic acid bis(erucylamide), gadolinium diethylenetriaminepentaacetic acid

bis(elaidylamide), gadolinium diethylenetriaminepentaacetic acid bis(linoleylamide), gadolinium diethylenetriaminepentaacetic acid bis(ricinoleylamide), gadolinium diethylenetriaminepentaacetic acid bis(petroselinyl), gadolinium diethylenetriaminepentaacetic acid bis(N-ethyl-N-oleylamide), gadolinium diethylenetriaminepentaacetic acid bis(N-methyl-N-oleylamide), gadolinium diethylenetriaminepentaacetic acid bis(linolenylamide), gadolinium diethylenetriaminepentaacetic acid bis(vaccenylamide), gadolinium diethylenetriaminepentaacetic acid bis(linderylamide), gadolinium diethylenetriaminepentaacetic acid bis(palmitoleylamide), gadolinium diethylenetriaminepentaacetic acid bis(palmitelaidylamide), gadolinium diethylenetriaminepentaacetic acid bis(myristoleylamide), and gadolinium diethylenetriaminepentaacetic acid bis(myristelaidylamide). The gadolinium complexes of the N-methyl, N-ethyl, and N-OH (where R_2= methyl, ethyl, or OH for each R_1) derivatives of these amides can also be included as examples.

B. Oil

The term "oil" is used herein in a general sense to identify a large class of physiologically acceptable substances whether of mineral, vegetable, animal, essential or synthetic origin. Thus, the term "oil" is used herein as applied to a wide range of substances that

are quite different in chemical nature. In the classification of oils by type or function, for example mineral oil is derived from petroleum and includes aliphatic or wax-based hydrocarbons, aromatic hydrocarbons or mixed aliphatic and aromatic based hydrocarbons. Also included in the mineral classification are petroleum-derived oils such as refined paraffin oil, and the like. In the vegetable classification, oils are chiefly derived from seeds or nuts and include drying oils such as linseed and tung oil; semidrying such as safflower and soy bean oils; nondrying such as castor, cottonseed and coconut oils and edible soap stocks such as palm and coconut oils. In the animal classification, oils usually occur as fats in tallow, lard and stearic acid sources. The liquid animal types include fish oils, oleic acid, sperm oil, etc. and they usually have a high fatty acid content. Included are some vegetable oils, such as olive, cottonseed, corn and peanut, as well as some special fish oils such as cod-liver, haliver, shark liver, and so forth which are used largely as medicines for their high vitamin content. A liquid fatty oil such as a mono-, di-, or triglyceride, or a mixture thereof, is the preferred oil. Medium chain triglycerides also serve as useful oils according to this invention.

c. <u>Fluorochemical</u>

In this description, "fluorochemical" or "PFC" is used to describe either a highly fluorinated organic compound of perfluorocarbon or fluorinated chemical.

Further, these terms are used interchangeably. The term "perfluorocarbon" includes a "cyclic" or "acyclic" compound of carbon. Substituted derivatives thereof are also included where fluorocarbons have other elements within their structures such as oxygen, hydrogen, nitrogen, chlorine, and bromine, etc. It should also be noted that the term "perfluorocarbon" is meant to include partially or substantially fluorinated compounds. This is permissible providing that the lack of complete replacement of all hydrogens does not affect the essential non-toxic characteristics of the preferred medical fluorocarbons of this invention. Among the perfluorocarbon compounds which may be employed are perfluorotributylamine (FC47), perfluorodecalin (PP5), perfluoromethyldecalin (PP9), perfluorooctylbromide, perfluorotetrahydrofuran (FC80), perfluoroether (PID) $[(CF_3)_2CFOCF_2(CF_2)_2CF_2OCF(CF_3)_2]$ perfluoroether (PIID) $[CF_3)_2CFOCF_2(CF_2)_6CF_2OCF(CF_3)_2]$,

perfluoropolymer (E3) $[CF_3CHF(OCF_2\underset{\displaystyle CF_3}{\underset{|}{C}}F)_2OCF_2CF_2CF_3]$,

perfluoropolymer (E4) $[CF_3CHF(OCF_2\underset{\displaystyle CF_3}{\underset{|}{C}}F)_3OCF_2CF_2CF_3]$ perfluoroetherpolymer (Fomblin Y/01), perfluorododecane, perfluorobicyclo[4.3.0.]nonane, perfluorotritrimethylblcyclohexane, perfluorotripropylamine, perfluoroisopropyl cyclohexane, perfluoroendotetrahydrodicyclopentadiene,

perfluoroadamantane, perfluoroexo-tetrahydrodicyclopentadiene, perfluorbicyclo[5.3.0.]decane, perfluorotetramethylcyclohexane, perfluoro-1-methyl-4--isopropylcyclohexane, perfluoro-n-butylcyclohexane, perfluorodimethylbicyclo[3.3.1.]nonane, perfluoro-1-methyl adamantane, perfluoro-1-methyl-4-t butylcyclohexane, perfluorodecahydroacenapthane, perfluorotrimethylbicyclo[3.3.1.]nonane, perfluoro-1-methyl adamantane, perfluoro-1-methyl-4-t butylcyclohexane, perfluorodecahydroacenaphthene, perfluorotrimethylbicyclo[3.3.1.]nonane, perfluoro-n-undecane, perfluorotetradecahydrophenanthrene, perfluoro-1,3,5,7-tetramethyladamantane, perfluorododecahydrofluorene, perfluoro-1-3-dimethyladamantane, perfluoro-n-octylcyclohexane, perfluoro-7-methyl bicyclo[4.3.0.] nonane, perfluoro-p-diisopropylcyclohexane, perfluoro-m-diisopropylcyclohexane, perfluoro-4-methyloctahydroquinolidizine, perfluoro-N-methyl-decahydroquinoline, F-methyl-1-oxadecalin, perfluorooctahydroquinolidizine, perfluoro 5,6-dihydro-5-decene, perfluoro-4,5-dihydro-4-octene, perfluorodichlorooctane and perfluorobischlorobutyl ether. Chlorinated perfluorocarbons, such as chloroadamantane and chloromethyladamantane as described in U.S. Patent No. 4,686,024 may be used. Such compounds are described, for example in U.S. Patent Nos. 3,962,439; 3,493,581,

4,110,474, 4,186,253; 4,187,252; 4,252,824; 4,423,077; 4,443,480; 4,534,978 and 4,542,147, European Patent Application Nos. 80710 and 158,996, British Patent specification 1,549,018 and German Offen. 2,650,586. Of course, it should be understood that mixtures of any of these highly fluorinated organic compounds may also be used in the emulsions and processes of this invention.

D. Surfactant

Surfactants are usually needed to form stable emulsions indicated above where the MRI agent has insufficient surfactant activity. Any suitable surfactant may be employed alone or in combination with other surfactants. For example, egg yolk phospholipids or Pluronics emulsifying agents may be used. Pluronics agents are block polymer polyols sold by Wyandotte, e.g., Pluronics F68, having a molecular weight of about 8,000, may be employed. Ethoxylates of cholesterol, diacyl glycerol and dialkyl ether glycerol are useful surfactants. Also, using backbones of cholesterol, diacyl glycerol or dialkyl ether glycerol, block copolymers are made by adding ethylene oxide, propylene oxide and ethylene oxide, in that order, in varying amounts to produce surfactants. In some applications for nonintravenous use, anionic or cationic surfactants may be used. The emulsions of this invention may contain alkylphosphoryl choline or alkylglycerophosphoryl choline surfactants described in Kaufman and Richard, U.S. Ser. No. 791,420, filed November 13, 1991. Specific examples

of these surfactants are 1,2-dioctylglycero-3-phosphoryl choline, 1,2-ditetradecylglycero-3-phosphoryl choline, 1,2-dihexadecylglycero-3-phosphoryl choline, 1,2-di-octadecylglycero-3-phosphoryl choline, 1-hexadecyl-2-tetradecylglycero-3-phosphoryl choline, 1-octadecyl-2-tetradecylglycero-3-phosphoryl choline, 1-tetradecyl-2-octadecylglycero-3-phosphoryl choline, 1-hexadecyl-2-octadecylglycero-3-phosphoryl choline, 1-2-dioctadecylglycero-3-phosphoryl choline, 1-octadecyl-2-hexadecylglycero-3-phosphoryl choline, 1-tetradecyl-2-hexadecylglycero-3-phosphoryl choline, 2,2-ditetradecyl-1-phosphoryl choline ethane and 1-hexadecyl-tetradecylglycero-3-phosphoryl choline. The 1,3-dialkyl glycerophosphoryl choline surfactants as described in Kaufman and Richard, U.S. Ser. No. 228,224, filed April 15, 1994 may also be used and the disclosure thereof is incorporated herein by references. Mixtures of these novel surfactants with other known surfactants may also be employed. Anionic surfactants include alkyl or aryl sulfates, sulfonates, carboxylates or phosphates. Cationic surfactants include such as mono-, di-, tri- and tetraalkyl or aryl ammonium salts. Non-ionic surfactants include alkyl or aryl compounds, whose hydrophilic part consists of polyoxyethylene chains, sugar molecules, polyalcohol derivatives or other hydrophilic groups. Zwitter-ionic surfactants may have a combination of the above anionic or cationic groups, and whose hydrophobic

part consists of any other polymer, such as polyisobutylene or polypropylene oxides.

E. Emulsion Characteristics

The emulsions of this invention are made by dispersing the above ingredients in water and homogenizing them. The oil and/or PFC are dispersed in the water and enhance the dispersion of the paramagnetic metal chelate complex. The surfactant enhances the dispersion by stabilization of the liquid phases. While dispersions may be generally referred to herein as emulsions, it should be understood that they may be considered solutions, micellar solutions, microemulsions, vesicular suspensions, or mixtures of all of these physical states. The PFC may be dispersed in the oil and the oil-PFC phase emulsified in the water. However, other possible interfaces and phases are within the scope of the invention. Accordingly, the term "emulsion" as used herein covers all these states and the surfactant is employed to enhance stable mixtures of these physical states of the fluorochemical, oil,paramagnetic metal chelate complex and water phases. For example, a fluorochemical and oil may be emulsified in water,as described in the Clark and Shaw European Pat. Appln. 87300454.3 and this application is incorporated herein by reference to describe suitable PFC/oil emulsions as MRI delivery agents.

The MRI emulsions of this invention are very fine, stable emulsions. The criterion for a "fine" emulsion is no visible solid matter microscopically (300-

400X) and less than 10 volume % of particles above about 0.8 μm ("CV"). The "poor" emulsions of comparative prior art, for example, have a large amount of huge (>5 μm) solids visible under the microscope, and greater than 10 volume % of particles above about 0.8 μm ("CV"). Reference is made to Figure 1 of the drawings which documents photographically the microscopic appearance of fine and poor emulsions at 300-400 X. In Figure 1, the fine emulsion contains 2% lecithin, 10% safflower oil and 5% GdDTPA-BOA of Example 8, Table 5, of this invention. The poor emulsion contains GdDTPA-BSA of Table 8 for comparison. Thus, these two complexes make markedly different quality emulsions although the complexes differ only in the unsaturation of the C_{18} chain.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts photographs of fine and poor emulsions at 300-400X.

Figures 1A and B are pre-contrast and post-contrast photographic MRI images of brain and liver.

Figure 2 depicts pre-contrast and post-contrast photographic MRI images of a liver.

The following non-limiting examples illustrate the various embodiments of this invention.

General Procedure for DTPA Bis(amides)

Under a static nitrogen atmosphere or a CaSO4 drying tube, a mechanically stirred mixture of diethylenetriaminepentaacetic (DTPA) dianhydride (1 mole) and anhydrous pyridine (2-24.7 mole; preferably 3.3 mole) in chloroform (0-3 L/mole of DTPA dianhydride; preferably 1 L/mole) was treated dropwise with a solution of the appropriate amine (2 mole) in chloroform (0-2.5 L/mole of amine; preferably 0.25 L/mole). In some cases, a mild exotherm was apparent. The resulting mixture was then heated at reflux (65°C w/o chloroform solvent) for 17-22 hours.

Workup Procedure A: After cooling to ambient temperature, the resulting reaction mixture was diluted with acetone (4-5 L/L of CHCl3) and cooled to 0°C. The resulting solid was filtered and washed with acetone. In some cases, the resulting solid was purified further by recrystallization from appropriate solvent to give the corresponding DTPA Bis(amide) (See Table 1 for more

details). These compounds were characterized by elemental analyses (see Table 2), infrared spectroscopy, proton and carbon nuclear magnetic resonance spectroscopy. High performance liquid chromatography was also used to assess purity on some derivatives.

Workup Procedure B: If no precipitate was obtained with acetone dilution on a small aliquot, the resulting reaction mixture was washed with 5% HCl to remove the pyridine and then with saturated brine solution. After drying over $MgSO_4$, concentration in vacuo yielded the crude DTPA Bis(amide) as a beige, glassy material (See Table 1 for more details). In some cases, column chromatography on silica gel with chloroform and methanol mixtures was used to remove trace impurities. These compounds were characterized further by elemental analyses (see Table 2), infrared spectroscopy, proton and carbon nuclear magnetic resonance spectroscopy. High performance liquid chromatography was also used to assess purity.

The above procedures were used to make various DTPA Bis(amide) ligands. The following Table 1 provides a variety of N R_1 R_2 groups under the above general formula in accordance with Workup A or B.

Table 1. DTPA Bisamide Ligands

R_1	R_2	Workup Procedure	Recryst Solvent	Yield	mp (°C)[a]
Stearyl ($C_{18}H_{37}$)	C_2H_5O	Chromatography	n/a	79%	168 (dec)
Oleyl ($C_{18}H_{35}$)	C_3H_7	Chromatography	n/a	96%	(glass)
Oleyl ($C_{18}H_{35}$)	C_4H_9	Chromatography	n/a	95%	(glass)
Oleyl ($C_{18}H_{35}$)	H	A	EtOH	45%	150-175[b]
Oleyl ($C_{18}H_{35}$)	H	A	EtOH	75%	150-180[b]
Oleyl ($C_{18}H_{35}$)	H	A	None	91%	178-184[b]
Stearyl ($C_{18}H_{37}$)	CH_3	A	EtOH[c]	81%	173-176
Stearyl ($C_{18}H_{37}$)	CH_3	A	EtOH[c]	89%	179-181
4-n-Hexadecylphenyl	H	A	DMF	97%[d]	190-194
Oleyl ($C_{18}H_{35}$)	Oleyl ($C_{18}H_{35}$)	B	Acetone	82%	115-150[b]
n-Dodecyl ($C_{12}H_{25}$)	H	A	MeOH[c]	96%[d]	180-183[e]
Geranyl ($C_{10}H_{17}$)	H	A	EtOH	91%	102-106
Farnesyl ($C_{15}H_{25}$)	H	A	EtOH	75%	140-142
Stearyl ($C_{18}H_{37}$)	H	A	AcOH/Et_2O	84%	155-158
Oleyl ($C_{18}H_{35}$)	Hexyl (C_6H_{13})	B		86%	
Erucyl ($C_{22}H_{43}$)	H	A	EtOH[c]	89%	168-172[e]
Ricinoleyl ($C_{18}H_{35}O$)	H	A	EtOH[c]	91%	75-80
Petroselinyl ($C_{18}H_{35}$)	H	A	EtOH[c]	96%	173-176[e]
Elaidyl ($C_{18}H_{35}$)	H	A	EtOH[c]	93%	173-178[e]
Linoleyl ($C_{18}H_{33}$)	H	A	EtOH[c]	91%	158-165
Oleyl ($C_{18}H_{35}$)	OH			99%	

a. Melting points were not sharp and generally softened and sweated at a lower temperature. Melted with decomposition.
b. Oleylamine and N,N-dioleylamine are invariably contaminated with the corresponding saturated amines (i.e. stearyl) and/or isomerized olefinic amines. These impurities presumably broaden the melting point.
c. In this case, the solid was simply slurried in hot solvent, rather than recrystallized to remove trace impurities, such as pyridine.
d. Yield prior to recrystallization of an analytical sample.
e. Analytical sample recrystallized from reagent alcohol.

Elemental analyses of the DTPA bis(amide) ligands were also performed and reported in the following Table 2.

Table 2. Elemental Analyses of DTPA Bisamide Ligands

R_1	R_2	Molecular Formula	Weight Per Cent Found (Calcd)			
			Carbon	Hydrogen	Nitrogen	Water
Oleyl	H	$C_{50}H_{93}N_5O_8$-0.2 H_2O	66.83 (67.03)	10.34 (10.51)	8.11 (7.82)	0.41 (0.41)
Stearyl	Methyl	$C_{52}H_{101}N_5O_8$-0.5H_2O [a]	67.00 (66.92)	11.14 (11.01)	7.47 (7.50)	0.89 (0.96)
Stearyl	Methyl	$C_{52}H_{101}N_5O_8$-1.0H_2O [a]	66.02 (66.27)	11.08 (11.02)	7.30 (7.43)	1.85 (1.9)
Stearyl	Stearyl	$C_{46}H_{89}N_5O_8$-1.0HCl-0.5H_2O [b]	62.00 (62.38)	10.13 (10.36)	7.66 (7.91)	0.52 (1.02)
4-n-Hexadecyl-phenyl	H	$C_{58}H_{97}N_5O_8$-1.0H_2O	68.94 (68.94)	9.52 (9.88)	6.86 (6.93)	0.8 (1.78)
Oleyl	Oleyl	$C_{86}H_{161}N_5O_8$-2.5H_2O	71.64 (71.82)	11.55 (11.63)	4.67 (4.87)	3.10 (3.13)
n-Dodecyl	H	$C_{38}H_{73}N_5O_8$	62.56 (62.69)	9.64 (10.11)	9.67 (9.62)	0.27 (0.0)
Geranyl	H	$C_{34}H_{57}N_5O_8$	61.30 (61.52)	8.71 (8.65)	10.67 (10.55)	2.71 (0.0)
Farnesyl	H	$C_{44}H_{73}N_5O_8$-2H_2O	62.94 (63.21)	8.87 (9.28)	8.21 (8.21)	3.25 (4.3)
Oleyl	C_3H_7	$C_{56}H_{105}N_5O_8$-0.5 H_2O	68.02 (68.25)	10.76 (10.84)	6.91 (7.11)	0.67 (0.91)
Oleyl	C_4H_9	$C_{58}H_{109}N_5O_8$-0.5 H_2O	68.51 (68.73)	11.06 (10.94)	6.85 (6.91)	0.32 (0.89)
Stearyl	C_2H_5O	$C_{54}H_{101}N_5O_{10}$-H_2O	65.28 (64.96)	11.00 (10.40)	6.19 (7.01)	4.81 (1.8)
Oleyl	Hexyl	$C_{62}H_{117}N_5O_8$-2HCl [b]	65.98 (65.69)	10.57 (10.57)	6.33 (6.33)	0.4 (0.0)
Erucyl	H	$C_{58}H_{109}N_5O_8$-0.5 H_2O	68.40 (68.73)	10.88 (10.94)	6.48 (6.91)	0.99 (0.88)
Petroselinyl	H	$C_{50}H_{93}N_5O_8$-H_2O	65.83 (65.98)	10.75 (10.52)	7.78 (7.69)	1.88 (1.97)
Ricinoleyl	H	$C_{50}H_{93}N_5O_{10}$-H_2O	64.10 (63.73)	10.16 (10.16)	7.53 (7.43)	1.60 (1.91)
Elaidyl	H	$C_{50}H_{93}N_5O_8$	66.97 (67.30)	10.47 (10.51)	7.84 (7.85)	0.24 (0.0)
Linoleyl	H	$C_{50}H_{89}N_5O_8$-0.5 H_2O	67.06 (66.93)	10.25 (10.11)	7.87 (7.81)	0.9 (1.0)
Oleyl	OH	$C_{50}H_{93}N_5O_{10}$- H_2O	63.27 (63.37)	9.97 (10.16)	7.33 (7.43)	0.54 (1.91)

a. Two different hydrates were isolated in this case.
b. As a result of the HCl workup, the isolated product was isolated as an HCl salt.

N-Mono-oleylamide of Diethylenetriaminepentaacetic Acid (DTPA-MOA)

Under a static nitrogen atmosphere, a mechanically stirred mixture of DTPA dianhydride (2.2-4.0 mole) and anhydrous pyridine (1.5-3.7 mole/mole of DTPA dianhydride) in anhydrous DMSO (1.5-1.7 L/mole of DTPA dianhyride) was heated to 70-85°C to dissolve most of the DTPA dianhydride. Neat oleylamine (1 mole) was then added dropwise to this solution at 60-65°C over a 5-15 minute period and the resulting mixture was held at 60-65°C for an additional hour. Water (18.6-24.9 mole) was added in one portion at 65-70°C and stirring continued for an additional hour. After cooling to room temperature, the mixture was diluted with chloroform to precipitate a tacky solid, which was filtered off with the aid of Celite. The red filtrate was concentrated in vacuum to remove the chloroform and most of the DMSO. The resulting residue was diluted with acetone to afford a tan solid, which was a mixture of the mono- and bis(amides) by TLC analysis [silica gel with 75:22:3 (V/V/V) $CHCl_3$:CH_3OH:H_2O]. These amides were readily separated by column chromatography on silica gel (100-200 mesh) using 75:22:3 (V/V/V) $CHCl_3$:CH_3OH:H_2O as eluant. The bisamide was isolated in 42-44% yield based on oleylamine. The mono(oleylamide) of DTPA was isolated as a white solid in 29-32% yield based on oleylamine after recrystallization from ethanol or methanol/ether mixtures in several crops. mp=205-8°C. This material was further characterized by high

performance liquid chromatography, infrared spectroscopy, proton and 13C nuclear magnetic resonance spectroscopy.

Anal. Calcd for $C_{32}H_{58}N_4O_9$-0.5H_2O: C, 58.97; H, 9.12%; N,8.60; H_2O, 1.37%. Found: C, 59.06%; H, 9.22%; N, 8.51%; H_2O, 1.35%.

General Procedure for Gadolinium Complexes with DTPA Bis(amide) Ligands

A stoichiometric equivalent of gadolinium oxide and the corresponding DTPA Bis(amide) in 75:22:3 (V/V/V) $CHCl_3$:CH_3OH:H_2O (≈0.1 mole of complex/L of solvent) was heated at reflux with stirring for 18-25 hrs. After cooling to ambient temperature, the solution was filtered through Celite to remove trace Gd_2O_3. The filtrate was concentrated in vacuo to yield an off-white solid or glass. The resulting solid was recrystallized from appropriate solvent or slurried in hot acetone as shown in Table 3 unless noted otherwise. In some cases, the resulting solid was dried in a vacuum oven at 50-65°C and 29" Hg vacuum overnight. Successful complexation was evident by the dissolution of Gd_2O_3 into the organic solvent mix, thin layer chromatography (TLC) relative to the free ligand and infrared spectroscopy. In general, high performance liquid chromatography (HPLC) of the isolated products were greater than 90% one component. In the case of the unsymmetrically N,N-disubstituted DTPA amides, four major peaks were evident by TLC and HPLC analyses suggesting isomers due to the two achiral nitrogen atoms in the complexed ligand and restricted rotation around amide bonds.

Gadolinium Complex of Bis((N,N-dioctyl)amide) of DTPA (GdDTPA-BDOA). Following the above procedure, resulting glass after concentration in vacuo was separated on a silica gel column with increasing ratios of methanol

to chloroform. Two different fractions were combined based on differences in 3000-3500 cm^{-1} infrared region. HPLC analyses indicated that these two fractions were the same. Elemental analyses showed different amounts of water and chloride for the two fractions suggesting that they were different hydrates containing varying amounts of chloroform and/or HCl and other contaminants as indicated below.

Fraction	Water (Wt%)	Cl (Wt%)	Carbon (Wt%)	Hydrogen (Wt%)	Nitrogen (Wt%)	Gd (Wt%)
1	0.97	4.54	54.2	8.99	6.55	12.82
2	1.80	9.61	48.01	8.05	6.01	12.99

Gadolinium Complex of Bis((N,N-dioleyl)amide) of DTPA (GdDTPA-BDOlA). The resulting glass after concentration in vacuo was separated on a silica gel column with 9:1 $CHCl_3$:CH_3OH to remove dioleylamine hydrochloride salt as an early eluting impurity. The desired product was isolated as a waxy solid after combining fractions and removal of the solvents on a rotary evaporator.

Gadolinium Complex with DTPA Mono(oleylamide) (GdDTPA-MOA). Under a static nitrogen atmosphere, a magnetically stirred mixture of DTPA mono(oleylamide) (5.0 gm; 7.8 mmole) and gadolinium oxide (1.45 gm; 4 mmole) in 100 ml of 75:22:3 (V/V/V) $CHCl_3$:CH_3OH:H_2O was heated at reflux for 25 hrs. The solution was suction filtered with the aid of Celite to remove trace Gd_2O_3. The filtrate was concentrated in vacuo to yield a beige solid. This solid was slurried in acetone, suction filtered and dried in a dessicator under vacuum; 6.1 gm (98% yield), mp>300°C. This gadolinium complex was characterized further by infrared spectroscopy and high performance liquid chromatography.

Anal. Calcd for $C_{32}H_{55}N_4O_9Gd$-2.0 H_2O: C, 46.14; H, 7.14%; N, 6.73; Gd, 18.88; H_2O, 4.32%. Found: C, 45.02%; H, 6.53%; N, 6.49%; Gd, 18.32; H_2O, 3.89%. The measured ratio of carbon to gadolinium (2.457) was in excellent agreement with the calculated ratio (2.444), suggesting that the material was contaminated with another element.

Table 3. Gd•DTPA Bisamide Complexes

Compound	R_1	R_2	Recryst Solvent	Yield	mp (°C)
GdDTPA-BOA	Oleyl	H	$CHCl_3$/MeOH/Acetone	85%	>300
GdDTPA-BDOA	Oleyl	Oleyl		>100%[a]	glass
GdDTPA-BMSA	Stearyl	Methyl	Acetone[b]	95%	276-82
GdDTPA-BHDPA	4-n-Hexadecyl-phenyl	H	Acetone	99%	>275
GdDTPA-BDOIA	Oleyl	Oleyl	Acetone[c]	72%	waxy solid
GdDTPA-BDDA	Dodecyl	H	EtOH/Acetone	80%	>300
GdDTPA-BGA	Geranyl	H	Acetone	97%	>300
GdDTPA-BFA	Farnesyl	H	Acetone	>100%[a]	d
GdDTPA-BSA	Stearyl	H	Acetone	100%	d
GdDTPA-BHOA	Oleyl	Hexyl	None	93%	d
GdDTPA-BRA	Ricinoleyl	H	Acetone	96	330-334 (dec)
GdDTPA-BPA	Petroselinyl	H	$CHCl_3$/MeOH/Acetone	94	333-335 (dec)
GdDTPA-BERA	Erucyl	H	$CHCl_3$/MeOH/Acetone	99%	332-334 (dec)
GdDTPA-BEA	Elaidyl	H	$CHCl_3$/MeOH/Acetone	98%	330-332 (dec)
GdDTPA-BLA	Linoleyl	H	$CHCl_3$/MeOH/Acetone	95%	>360
GdDTPA-BPOA	Oleyl	C_3H_7	$CHCl_3$/MeOH/Acetone	90%	160 (dec)
GdDTPA-BBuOA	Oleyl	C_4H_9	Chromatography	60%	140 (dec)
GdDTPA-BHESA	Stearyl	C_2H_5O	Chromatography	96%	198-200 (dec)
GdDTPA-BEOA	Oleyl	C_2H_5	Acetone[b]	99%	>245
GdDTPA-BBOA	Oleyl	C_7H_7	none	98%	>270
GdDTPA-BOHA	Oleyl	OH	Chromatography	63%	245 (dec)

a. The crude product was obviously contaminated with solvent.
b. The crude product was dissolved in hot acetone and continuously stirred with a magnetic stirrer while cooling to room temperature to yield a white solid.
c. The resulting solid isolated after column chromatography on silica gel was slurried in acetone at room temperature and filtered.
d. Not determined

Table 4. Elemental Analyses of Gadolinium DTPA Bis-Amide Complexes

Compound	R_1	R_2	Molecular Formula	Weight Per Cent Found (Calcd)				
				C	H	N	Gd	Water
GdDTPA-BOA	Oleyl	H	$C_{50}H_{90}N_5O_8Gd$-H_2O	56.17 (56.41)	8.51 (8.71)	6.33 (6.58)	15.44 (14.77)	0.21 (1.69)
GdDTPA-BMSA	Stearyl	Methyl	$C_{52}H_{98}N_5O_8Gd$-$2H_2O$	55.81 (56.03)	9.16 (9.22)	5.98 (6.28)	14.44 (14.11)	2.96 (3.23)
GdDTPA-BHDPA	4-n-Hexa-decylphenyl	H	$C_{58}H_{94}N_5O_8Gd$-$1.5H_2O$	59.18 (59.36)	8.39 (8.33)	5.82 (5.97)	13.67 (13.40)	2.51 (2.30)
GdDTPA-BDOlA	Oleyl	Oleyl	$C_{86}H_{158}N_5O_8Gd$-$0.5H_2O$	66.02 (66.36)	10.22 (10.3)	4.19 (4.5)	10.09 (10.1)	0.47 (0.58)
GdDTPA-BDDA	Dodecyl	H	$C_{38}H_{70}N_5O_8Gd$-$0.5H_2O$	51.27 (51.73)	8.13 (8.0)	8.06 (7.94)	16.83 (17.82)	0.83 (1.0)
GdDTPA-BGA	Geranyl	H	$C_{34}H_{54}N_5O_8Gd$-$0.5H_2O$	49.09 (49.38)	6.57 (6.57)	8.32 (8.32)	19.68 (19.01)	0.8 (1.08)
GdDTPA-BFA	Farnesyl	H	$C_{44}H_{70}N_5O_8Gd$-H_2O	52.48 (54.35)	7.32 (7.46)	7.18 (7.20)	13.19 (16.17)	1.6 (1.85)
GdDTPA-BSA	Stearyl	H	$C_{50}H_{94}N_5O_8Gd$-$2H_2O$	55.61 (55.26)	8.99 (9.09)	6.47 (6.44)	14.77 (14.47)	3.90 (3.32)
GdDTPA-BHOA	Oleyl	Hexyl	$C_{62}H_{114}N_5O_8Gd$-$4H_2O$	57.87 (57.86)	9.17 (9.56)	5.37 (5.44)	12.62 (12.22)	2.73 (5.60)
GdDTPA-BPA	Petroselinyl	H	$C_{50}H_{90}N_5O_8Gd$-$0.5H_2O$	56.60 (56.90)	8.54 (8.69)	6.66 (6.63)	15.46 (14.90)	0.40 (0.85)
GdDTPA-BRA	Ricinoleyl	H	$C_{50}H_{90}N_5O_{10}Gd$-$0.5H_2O$	54.90 (55.22)	8.52 (8.43)	6.53 (6.44)	14.87 (14.46)	0.58 (0.82)
GdDTPA-BERA	Erucyl	H	$C_{58}H_{106}N_5O_8Gd$-$4.5\ H_2O$	55.83 (56.18)	9.23 (9.35)	5.32 (5.65)	13.34 (12.68)	6.25 (6.54)
GdDTPA-BLA	Linoleyl	H	$C_{50}H_{86}N_5O_8Gd$-H_2O	56.17 (56.63)	8.28 (8.36)	6.63 (6.6)	15.11 (14.83)	1.45 (1.69)
GdDTPA-BEA	Elaidyl	H	$C_{50}H_{90}N_5O_8Gd$-$0.5H_2O$	56.55 (56.90)	8.75 (8.69)	6.24 (6.63)	15.06 (14.9)	0.72 (0.85)
GdDTPA-BPOA	Oleyl	C_3H_7	$C_{56}H_{102}N_5O_8Gd$-$1.5\ H_2O$	58.05 (58.10)	9.09 (9.14)	5.87 (6.05)	6.56 (13.58)	2.16 (2.33)
GdDTPA-BBuOA	Oleyl	C_4H_9	$C_{58}H_{106}N_5O_8Gd$ -1 H_2O-0.5 HCl	58.04 (57.86)	9.19 (9.17)	5.57 (5.82)	6.30 (13.06)	2.17 (2.24)
GdDTPA-BHESA	Stearyl	C_2H_5O	$C_{54}H_{101}N_5O_{10}Gd$ -3.75 H_2O-0.75 HCl	54.74 (54.88)	8.93 (9.07)	5.41 (5.71)	12.35 (12.83)	5.34 (5.51)
GdDTPA-BEOA	Oleyl	C_2H_5	$C_{54}H_{98}N_5O_8Gd$-H_2O	57.76 (57.88)	9.09 (8.99)	6.16 (6.25)	13.60 (14.03)	1.52 (1.61)
GdDTPA-BBOA	Oleyl	C_7H_7	$C_{42}H_{76}N_5O_8Gd$-H_2O	52.43 (52.86)	8.43 (8.24)	7.18 (7.34)	17.14 (16.48)	1.97 (1.89)
GdDTPA-BOHA	Oleyl	OH	$C_{50}H_{90}N_5O_{10}Gd$-H_2O	54.51 (54.77)	8.57 (8.46)	6.41 (6.39)	14.37 (14.34)	1.58 (1.64)

Preparations of GdDTPA Bis(oleylamide) Emulsions

All GdDTPA Bis(oleylamide) experimental emulsions in Table 5 were prepared in 28 mL volumes using an M-110S microfluidizer. The equipment was flushed with deionized water between each emulsion formulation. The emulsion components: Water, safflower oil, PFDCO (perfluorodichlorooctane), gadolinium complex and lecithin were weighed into a 30 mL capacity blender cup. The water component contained approximately 300μl of 5% $NaCO_3$ to adjust the material pH to a physiological range. On average, emulsions showed a 1.5 pH drop during sterilization. The mix was blended for 30-60 seconds depending on the concentration of water in the sample. The sample was transferred to the reservoir of the microfluidizer and emulsified for three minutes. To prevent the emulsions from heating excessively during homogenation, the shear valve and mixing coil were immersed in a room temperature water bath during processing. The final temperature of the emulsion samples was approximately 35°C. Completed emulsions were bottled in 30mL serum vials, with a head of nitrogen gas. Autoclave conditions were: 4-7 minutes heat up to sterilization temperature, sterilization at 121°C for 15 minutes and a 15 minute pressurized cold water cool down to final temperatures at 25-30°C.

In general, with reference to Table 5, the quality of the emulsions was excellent, with the exceptions noted. Microscopically, emulsions containing

no oil component showed incomplete dispersion of the GdDTPA-Bis(amide) complex. Emulsions exhibited high viscosity (or a gel like consistency) when either the safflower oil or the PFC content was greater than about 25% w/v or about 55 v/v%, respectively. The gadolinium complex exhibited surfactant activity during emulsification, except foaming occurred. Upon separation from the foam, a high quality stable emulsion was isolated. Therefore, a separate surfactant may be eliminated in certain cases where a chelate complex exhibits sufficient surfactant activity.

Table 5. Gadolinium DTPA-BOA Emulsions

Emulsion	Lec.	Oil	PFC	Gd	pH	pH Post	Osm	Osm Post	Visc	Visc Post	PSD	PSD Post	CM	CM Post	CV	CV Post
1	2.0%	9.9%	0.0%	4.9%	8.07	6.80	318	320	1.74	1.80	158	157	1.097	0.754	0.027	0.117
2	2.0%	25.0%	0.0%	5.1%	8.08	6.60	312	308	3.45	3.96	127	127	2.250	1.190	0.027	0.015
3	2.0%	49.5%	0.0%	5.0%	8.30	7.01	326	296	-	-	140	143	2.250	1.110	0.019	0.029
4	0.5%	9.8%	0.0%	5.0%	8.16	7.08	303	300	1.51	1.74	182	185	0.895	0.678	0.055	0.080
5	0.5%	23.9%	0.0%	5.0%	8.30	6.77	356	357	3.71	3.77	134	135	0.628	1.139	0.008	0.108
6	9.8%	24.6%	0.0%	5.2%	8.47	7.10	379	262	5.74	20.50	101	301	0.978	12.200	0.009	100
7	2.0%	10.1%	0.0%	2.0%	8.10	7.21	340	344	1.10	1.39	180	179	1.106	0.815	0.035	0.044
8	2.0%	10.0%	0.0%	5.0%	8.35	7.10	306	298	1.51	1.64	186	184	0.747	0.823	0.120	0.057
9	2.0%	9.8%	0.0%	9.9%	8.48	7.22	324	323	2.59	3.47	155	161	1.240	0.732	0.194	0.041
10	2.0%	0.0%	9.9%	5.0%	8.03	6.57	322	315	1.31	1.45	39	125	1.250	0.840	0.233	0.028
11	2.0%	0.0%	24.8%	5.0%	8.39	6.97	367	377	3.26	3.51	134	155	0.628	0.741	0.053	0.029
12	2.0%	0.0%	39.7%	5.0%	8.73	7.32	396	296	18.70	10.10	111	170	1.120	0.780	0.017	0.020
13	0.5%	0.0%	24.4%	4.9%	9.02	7.18	661	666	3.41	3.12	117	161	1.140	1.140	0.022	0.103
14	10.1%	0.0%	25.0%	5.0%	8.43	7.22	389	393	6.35	6.71	74	119	1.423	1.680	0.101	0.201
15	2.0%	0.0%	9.6%	2.1%	8.61	7.47	593	585	1.29	1.03	82	131	1.120	0.992	0.209	0.025
16	2.0%	0.0%	10.4%	10.0%	8.53	7.10	485	483	2.02	2.20	73	111	1.590	1.050	0.149	0.060
17	2.0%	1.9%	10.0%	2.0%	7.80	6.72	318	281	1.33	1.39	133	152	1.121	0.886	0.016	0.072
18	2.0%	2.0%	9.8%	5.0%	7.95	6.65	311	324	1.41	1.61	171	160	0.740	0.740	0.064	0.203
19	2.1%	9.1%	1.2%	5.1%	8.66	7.35	353	329	1.51	2.22	114	109	1.006	0.628	0.029	0.164
20	3.0%	10.2%	39.8%	5.0%	8.79	7.50	254	126	-	-	99	112	1.291	2.127	0.026	0.197
21	3.0%	39.7%	10.2%	5.0%	8.69	7.40	156	214	-	-	119	131	0.992	2.279	0.018	0.200
22	2.1%	10.1%	0.0%	5.0%	8.74	7.17	297	295	1.79	1.84	109	92	1.124	1.256	0.054	0.068
23	2.1%	2.1%	10.1%	5.2%	8.75	7.26	364	379	1.99	2.59	84	106	1.188	1.108	0.026	0.032
24	2.0%	0.0%	11.8%	4.9%	8.94	7.46	307	297	1.69	1.77	99	120	0.938	1.171	0.068	0.044
25	2.0%	9.9%	0.0%	5.0%	8.33	6.73	327	328	2.62	2.56	106	102	0.925	1.403	0.032	0.132
26	2.0%	1.9%	10.0%	5.0%	10.27	7.70	324	324	2.44	2.45	200	131	1.546	1.273	0.086	0.179
27	2.0%	9.9%	0.0%	5.0%	8.33	6.73	327	328	2.62	2.56	106	102	0.794	5.613	0.039	41.24

Visc = viscosity in centipose (cP)
CM = mean particle size above 0.78 µm
Osm = osmolality (mOs/kg)

PSD = submicron mean particle size (nm)
CV = volume percent of particles above 0.78 µm
post = post-sterilization values (121°C for 15 minutes)

With reference to the above Table 5, Examples 3 and 21 demonstrated a gelatinous consistency; and Examples 6, 10 and 17 separated into two layers upon storage. With respect to Examples 22, 23 and 24, the surfactant was 1,3-dihexyldecylglycero-2-phosphoryl choline. Furthermore, the surfactant employed in Examples 25, 26 and 27 was Pluronic F68 and, with respect to Example 27, it was of a pasty consistency.

Using the above general procedure for making the GdDTPA bis(oleylamide) emulsions, other Gd or Mn chelate complex emulsions were made with oil and/or PFC dispersed oil phases and with various ligands for the NR_1R_2 group of the above general formula. The key to the acronyms for the ligands are shown in Table 6.

With reference to Table 6, very fine and stable emulsions were obtained for complexes having an unsaturated group with a single, double or plurality (2 or greater) of double bond(s) and at different locations in the group. Branched or straight chain groups are also suitable.

Table 6. Key to Ligands

BOA = bis(oleylamide)
BHEOA = bis(N-hydroxyethyl-N-oleylamide)
BSHA = bis(N-stearyl-N-hydroxylamine)
BEOA = bis(N-ethyl-N-oleylamide)
BHOA = bis(N-hexyl-N-oleylamide)
BGA = bis(geranylamide)
BFA = bis(farnesylamide)
BHDPA = bis(N-hexadecylphenylamide)
BOHA = bis(N-oleyl-N-hydroxylamine)
BEA = bis(elaidylamide)
BTDA = bis(tetradecylamide)
BRA = bis(ricinoleylamide)
BDOlA = bis((N,N-dioleyl)amide)
BPA = bis(petroselinyl)

BMSA = bis(N-methyl-N-stearylamide)
MOA = mono(oleylamide)
BHESA = bis(N-hydroxyethyl-N-stearylamide)
BBOA = bis(benzyloleylamide)
BSA = bis(stearylamide)
BBuOA = bis(N-butyl-N-oleylamide)
BPOA = bis(N-propyl-N-oleylamide)
BERA = bis(erucylamide)
BDDA = bis(dodecylamide)
BHDA = bis(hexadecylamide)
BLA = bis(linoleylamide)
BDOA = bis((N,N-dioctyl)amide)
BODP = bis(N-octadecyl-N-propanediolamide)

The MRI emulsions of this invention that have been made in accordance with the above detailed description were characterized into various categories of emulsions for comparison with other paramagnetic metal ion chelate complexes outside the scope of this invention. According to this invention, the paramagnetic metal chelate complexes that make fine emulsions have been categorized as those in accordance with the above general formula where A.) R_1 is a single straight or branched long carbon chain (C_{10}-C_{30}) on the nitrogen that is unsaturated (or has multiple unsaturations), or B.) R_1 is a long straight or branched carbon chain (C_{10}-C_{30}) on the nitrogen that is unsaturated (or has multiple unsaturations) and R_2 is a short chain (C_1-C_2) and C.) R_1 is a long straight or branched carbon chain (C_{10}-C_{30}) on the nitrogen that is unsaturated (or has multiple unsaturations) and has a hydroxyl group on the nitrogen. The categories of emulsions and complexes of this invention that make fine emulsions are compared to other emulsions and complexes that make poor emulsions as reported in Table 7.

Table 7. Categories of Emulsions and Complexes

R_1	R_2	Category #
Poor (comparative)		
$C_{\geq 10}$ - Saturated	H	1
$C_{\geq 10}$ - Saturated	$C_{\geq 1}$ - Saturated	2
$C_{\geq 10}$ - Unsaturated	$C_{\geq 2}$ Sat./Unsat.	3
Fine (invention)		
$C_{\geq 10}$ - Unsaturated	H	4
$C_{\geq 10}$ - Unsaturated	$C_{\leq 2}$ Alkyl	5
$C_{\geq 10}$ - Unsaturated	OH	6

As may be determined from the above Table 7, the emulsions and chelate complexes of categories 4-6 are representative of those MRI chelate complexes that make fine emulsions in accord with this invention. Those emulsions and chelate complexes of categories 1-3 make poor emulsions. The tabular summaries for each of the above categories 1-6 are reported in the following Tables 8-13.

Table 8. Comparative Category #1 (single saturated chain)

Active Component	% lec./% oil	Quality	R_1	R_2	Visc	PSD	CM	CV
5% GdDTPA-BSA	2/10	Solids	$C_{18}H_{37}$	H	35.70	194	6.54	48.4
5% GdDTPA-BSA	2/5	Solids	$C_{18}H_{37}$	H	*	212	8.28	98.8
5% GdDTPA-BSA	2/20	Solids	$C_{18}H_{37}$	H	*	191	7.11	72.8
5% GdDTPA-BSA	4/10	Solids	$C_{18}H_{37}$	H	9.44	194	7.73	82.4
5% GdDTPA-BSA	4/5	Solids	$C_{18}H_{37}$	H	9.77	188	7.83	86.6
5% GdDTPA-BSA	4/20	Solids	$C_{18}H_{37}$	H	9.52	269	5.85	32.9
5% GdDTPA-BDDA	2/10	Solids	$C_{12}H_{25}$	H	1.8	210	2.34	19.8
5% GdDTPA-BHDA	2/10	Solids	$C_{16}H_{33}$	H	2.59	184	3.55	39.8
5% GdDTPA-BTDA	2/10	Solids	$C_{14}H_{29}$	H	1.55	196	2.73	18.24
5% GdDTPA-BHDPA	2/10	Solids	$C_{22}H_{37}$	H	2.82	195	6.63	100

FOOTNOTE FOR TABLES 8-13
Quality = as viewed at 1200X
Visc. = viscosity in centipose (cP)
CM = mean particle size above 0.78 µm

PSD = submicron mean particle size (nm)
CV = volume percent of particles above 0.78 µm

Table 9. Comparative Category #2 (two saturated chains)

Active Component	% lec./% oil	Quality	R_1	R_2	Visc	PSD	CM	CV
5% GdDTPA-BMSA	2/10	Solids	$C_{18}H_{37}$	CH_3	2.04	532	2.41	12.52
5% MnEDTA-BODP	2/10	Solids	$C_{18}H_{37}$	$C_3H_7O_2$	2.87	187	4.139	35.40
5% GdDTPA-BDOA	2/10	Failed	C_8H_{17}	C_8H_{17}				

Table 10. Comparative Category #3 (one unsaturated chain, one long chain C>2)

Active Component	% lec./% oil	Quality	R_1	R_2	Visc	PSD	CM	CV
5% GdDTPA-BDOIA	2/10	Failed	$C_{18}H_{35}$	$C_{18}H_{35}$	--	--	--	--
5% GdDTPA-BBOA	2/10	Failed	$C_{18}H_{35}$	C_7H_7	--	--	--	--
5% GdDTPA-BPOA	2/10	Solids	$C_{18}H_{35}$	C_3H_7	24.4	569	7.11	43.1
5% GdDTPA-BBuOA	2/10	Solids	$C_{18}H_{35}$	C_4H_9	2.17	*	9.12	54.4
5% GdDTPA-BHOA	2/10	Failed	$C_{18}H_{35}$	C_6H_{13}	--	--	--	--

Table 11. Invention Category #4 (one unsaturated chain)

Active Component	% Iec./% oil	Quality	R_1	R_2	Visc	PSD	CM	CV
5% GdDTPA-BOA	2/10	Excellent	$C_{18}H_{35}$	H	1.64	184	0.82	0.44
2% GdDTPA-BOA	2/10	Excellent	$C_{18}H_{35}$	H	1.39	179	0.82	0.44
10% GdDTPA-BOA	2/10	Excellent	$C_{18}H_{35}$	H	3.47	161	<0.73	0.40
5% GdDTPA-BOA	0.5/10	Excellent	$C_{18}H_{35}$	H	1.74	185	<0.68	0.80
5% GdDTPA-MOA**	2/10	Excellent	$C_{18}H_{35}$	H	1.66	134	0.852	0.88
5% GdDTPA-BFA	2/10	Excellent	$C_{15}H_{25}$	H	1.70	167	1.31	0.32
5% GdDTPA-BGA	2/10	Very Good	$C_{10}H_{17}$	H	1.35	185	1.29	1.92
5% GdDTPA-BERA	2/10	Very Good	$C_{22}H_{43}$	H	2.29	162	1.29	0.32
5% GdDTPA-BEA	2/10	Very Good	$C_{18}H_{35}$	H	3.12	142	2.04	4.68
5% GdDTPA-BLA	2/10	Excellent	$C_{18}H_{33}$	H	1.67	116	1.01	0.28
5% GdDTPA-BPA	2/10	Very Good	$C_{18}H_{35}$	H	1.54	124	0.83	0.24
5% GdDTPA-BRA	2/10	Good	$C_{18}H_{35}O$	H	4.43	108	1.4	2.68

Table 12. Invention Category #5 (one unsaturated chain, one alkyl C≤2)

Active Component	% lec./% oil	Quality	R1	R2	Visc	PSD	CM	CV
5% GdDTPA-BEOA	2/10	Excellent	$C_{18}H_{35}$	C_2H_5	1.87	206	0.88	0.36

Table 13. Invention Category #6 (one -OH, and one unsaturated chain C≥10)

Active Component	% lec./% oil	Quality	R1	R2	Visc	PSD	CM	CV
5% GdDTPA-BOHA	2/10	Excellent	$C_{18}H_{35}$	OH	2.62	165	1.51	0.32

With respect to Comparative Category #1 as represented by Table 8, it was found that where R_1 was a single saturated chain and R_2 was hydrogen as represented by GdDTPA-BSA, poor emulsions were made despite a variety of compositions containing a surfactant lecithin, oil and PFDCO. Furthermore, with respect to those emulsions indicated by an asterisk(*), they were too viscous to measure. With reference to Comparative Categories #2 and #3 in Tables 9 and 10, where R_1 and R_2 were two saturated chains or one unsaturated chain and one long chain C)2, the emulsions had huge solids or simply failed to emulsify. In Table 10, the asterisk (*) indicates that the emulsion cracked upon sterilization and the particle sizes were too large to be measured by sub-micron particle sizer.

In contrast, the invention is represented by Tables 11, 12 and 13 where Categories Nos. 4, 5 and 6 are shown. In other words, where R_1 was a C_{10}-C_{30} unsaturated chain and R_2 was either hydrogen, hydroxyl or a C_1-C_2 alkyl, excellent emulsions were obtained.

Furthermore, at the present time, the most preferred paramagnetic metal chelate complex is GdDTPA-BOA which provides for an excellent emulsion with CVs above 0.8 micron being less than 1%. In addition, the monoamide version of GdDTPA-BOA also provided an excellent emulsion. With reference to Table 5, a summary of the many formulations is provided for the most preferred compound

GdDTPA-BOA having different compositions of oil alone, or combinations of oil and PFDCO, or PFDCO alone. For the most part, all of the emulsions in Table 5 were excellent with CVs above 0.8 micron again less than 1%, with the noted exceptions.

With respect to Tables 14, 15 and 16, the stabilities of the emulsions made with GdDTPA-BOA at 40°C (accelerated), 0°C (refrigerated) and 25°C (room temperature) were determined. As may be determined with respect to these tables, emulsions of this invention provided excellent stability over the period of time indicated. However, those emulsions that were noted above to be poor emulsions typically become a gel (solid mass) by three months in refrigeration and thus no data can be measured for these. Also, the photographs of Figure 1 at 400 X magnification are representative of the "fine" and "poor" emulsions. At a magnification of 400 x, a 10 micron particle will be about 4mm in the photo.

Table 14. 40 ºC Stability Data for GdDTPA-BOA

2% Lecithin/10% oil/5% Complex	0 Time	2 Weeks	4 Weeks	6 Weeks
GdDTPA-BOA by HPLC (%w/w)	4.85	4.70	4.70	5.13
pH	6.78	6.53	7.14	6.47
Viscosity (cP)	1.87	1.84	2.02	1.87
Submicron mean particle size (nm)	165	167	167	169
Mean particle size above 0.78 µm (µm)	0.93	0.63	1.09	0.81
Volume percent of particles above 0.78 µm	0.16	0.56	0.32	0.56
Visual inspection	normal	normal	normal	normal
Microscopic exam	excellent	excellent	excellent	excellent

Table 15. 4 ºC Stability Data for GdDTPA-BOA

2% Lecithin/10% oil/5% Complex	0 Time	3 Months	6 Months
GdDTPA-BOA by HPLC (%w/w)	4.85	5.36	5.89
pH	6.78	6.95	6.73
Viscosity (cP)	1.87	2.07	2.15
Submicron mean particle size (nm)	165	170	169
Mean particle size above 0.78 µm (µm)	0.93	1.05	0.99
Volume percent of particles above 0.78 µm	0.16	0.52	0.16
Visual inspection	normal	normal	normal
Microscopic exam	excellent	excellent	excellent

Table 16. 25 °C Stability Data for GdDTPA-BOA

2% Lecithin/10% oil/5% Complex	0 Time	3 Months	6 Months
GdDTPA-BOA by HPLC (% w/w)	4.85	5.31	5.96
pH	6.78	6.81	6.61
Viscosity (cP)	1.87	2.15	1.87
Submicron mean particle size (nm)	165	169	166
Mean particle size above 0.78 µm (µm)	0.93	0.84	0.93
Volume percent of particles above 0.78 µm	0.16	0.72	0.12
Visual inspection	normal	normal	normal
Microscopic exam	excellent	excellent	excellent

The MRI utilities of the emulsions have been determined by using an emulsion containing 5% of GdDTPA-BOA to improve 3D time - of - flight angiography in a rabbit. Figure 1A shows a number of major cerebral arteries and branches that can be easily visualized in the post-contrast image that could not be appreciated before administration of the chelate complex. Angiography is often difficult to perform in the liver and Figure 1B shows that little or no vascular detail can be seen in the pre-contrast liver, whereas with the post-contrast GdDPTA-BOA emulsion of this invention, visualization of vascular structures is allowed within this organ. Thus, with reference to both the brain and the liver, a 10 μmole of gadolinium per kg dose was administered intravenously and the enhancement effect on the angiograms persisted for at least one hour. Both images were collected with the standard 3D time - of - flight imaging sequence on a General Electric Signa whole body clinical scanner operating at 1.5 Tesla.

An emulsion containing 4.2% of GdDPTA-MOA was used to enhance the liver of a rabbit. Figure 2 shows that nearly 150% enhancement occurs in the liver after intravenous administration of a 10 μmole of gadolinium per/kg dose. The enhancement effect on the liver persisted for at least one hour. The images were collected with a standard T_1-weighted spin-echo imaging sequence on a General Electric Signa whole body clinical scanner 3operating at 1.5 Tesla.

For comparison with the emulsions of this invention, Examples I and VII were reproduced from U.S. Patent 5,120,527, mentioned in the above background of this invention. Although the emulsions made under this '527 patent according to these procedures do not have visible solids, they have very large particles on the order of 10 to about 30 microns and hence are unacceptable for IV use. With respect to the emulsion containing Geritol®, the composition contained 60mL Geritol®, 150mL melted ice cream, 250mL milk and 100mL corn oil; with other properties including viscosity of 6.05 cp, CM of 8.17 microns and CV of 83.1%. The Geritol® emulsion also cracked upon sterilization. The GdDTPA emulsion contained 0.5mole (1.0mL) of GdDTPA, 150mL melted ice cream, 250mL milk and 100mL corn oil; with the other properties of the emulsion including a viscosity with 8.18cp, CM of 16.3 microns and CV of 71.8%. In summary, the emulsions of the '527 patent are unacceptable for IV use and do not have the versatility of the emulsions of this invention. They also lack stability upon sterilization as evidenced by the above experiments.

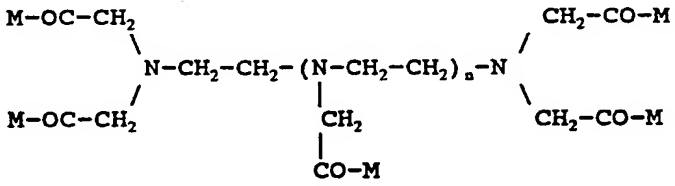
In view of the above detailed description, other variations or modifications may be made without departing from the spirit and scope of this invention.

What is claimed is:

CLAIMS

1. A physiologically acceptable emulsion for enhancement of MRI imaging comprising water, a dispersed oil phase and a paramagnetic metal complex having a C_{10}-C_{30} unsaturated aliphatic group.

2. A physiologically acceptable emulsion for enhancement of MRI imaging comprising water, a dispersed oil phase and a complex of a paramagnetic metal ion and an organic chelator having the formula



wherein from 2 to 5 M groups are hydroxyl, n=0 to 2, and any remaining M group is NR_1R_2, each R_1 is a C_{10}-C_{30} unsaturated aliphatic group and R_2 is hydrogen, hydroxyl or a C_1-C_2 alkyl.

3. The physiologically acceptable emulsion of claim 2 wherein said metal ion is a lanthanide element of atomic numbers 58-70 or a transition metal of atomic numbers 21-29, 42 or 44.

4. The physiologically acceptable emulsion of claim 2 wherein said metal ion is selected from a group consisting Gd(III), Mn(II), iron and dysprosium.

5. The physiologically acceptable emulsion of claim 2 wherein said organic chelator is an acid selected from the group consisting of ethylenediaminetetraacetic acid and diethylenetriaminepentaacetic acid.

6. The physiologically acceptable emulsion of claim 2 wherein said organic chelator is a monoamide or a bisamide of an organic acid selected from a group consisting of diethylenetriaminepentaacetic acid and ethylenediaminetetraacetic acid.

7. The physiologically acceptable emulsion of claim 2 wherein each R_1 is C_{14}-C_{22}.

8. The physiologically acceptable emulsion of claim 2 wherein the organic chelator is a mono or bisamide where R_1 is selected from the group consisting of oleyl, farnesyl, geranyl, erucyl, elaidyl, linoleyl, ricinoleyl, petroselinyl, linolenyl, vaccenyl, linderyl, palmitoleyl, palmitelaidyl, myristoleyl, and myristelaidyl, and where R_2 is selected from the group consisting of methyl, ethyl, and hydroxyl.

9. The physiologically acceptable emulsion of claim 2 wherein said complex is gadolinium diethylenetriaminepentaacetic acid bis(oleylamide).

10. The physiologically acceptable emulsion of claim 2 wherein said chelate complex is gadolinium diethylenetriaminepentaacetic acid mono(oleylamide).

11. The emulsion of claim 2 that is stable after heat sterilization with less than 10 volume % of particles above about 0.8 micron.

12. The emulsion of claim 2 wherein the oil phase contains about 5 to about 25% w/v oil or about 5 to about 55% v/v fluorochemical.

13. The emulsion of claim 2 wherein the oil is selected from the group consisting of mono-, di- and triglycerides, and mixtures thereof.

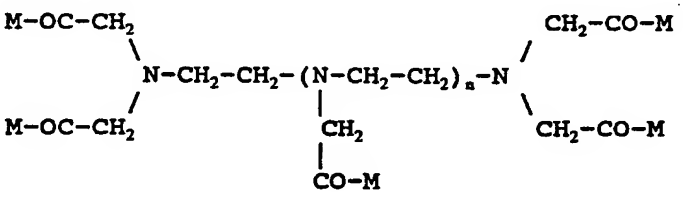
14. The emulsion of claim 12 wherein the surfactant is present in an amount from about 0.5 to about 10% by weight of the emulsion.

15. The physiologically acceptable emulsion of claim 2 wherein the chelate complex is selected from the group consisting of gadolinium diethylenetriaminepentaacetic acid bis(oleylamide), gadolinium diethylenetriaminepentaacetic acid mono(oleylamide), gadolinium diethylenetriaminepentaacetic acid bis(farnesylamide), gadolinium diethylenetriaminepentaacetic acid bis(geranylamide), gadolinium diethylenetriaminepentaacetic acid bis(erucylamide), gadolinium diethylenetriaminepentaacetic acid bis(elaidylamide), gadolinium diethylenetriaminepentaacetic acid bis(linoleylamide), gadolinium diethylenetriaminepentaacetic acid bis(ricinoleylamide), gadolinium diethylenetriaminepentaacetic acid bis(petroselinyl), gadolinium diethylenetriaminepentaacetic acid bis(linolenylamide), gadolinium diethylenetriaminepentaacetic acid bis(vaccenylamide), gadolinium diethylenetriaminepentaacetic acid bis(linderylamide), gadolinium diethylenetriaminepentaacetic acid bis(palmitoleylamide), gadolinium diethylenetriaminepentaacetic acid bis(palmitelaidylamide), gadolinium diethylenetriaminepentaacetic acid bis(myristoleylamide), gadolinium diethylenetriaminepentaacetic acid bis(myristelaidylamide), and the N-methyl, N-ethyl, and N-OH derivatives of said gadolinium complexes.

16. A physiologically acceptable emulsion for intravenous administration and enhancement of MRI imaging comprising water, a dispersed oil phase and a paramagnetic metal complex having a C_{10}-C_{30} unsaturated aliphatic group, said emulsion having an average particle size less than about 1 micron.

17. The physiologically acceptable emulsion of claim 16 having an average particle size on the order of about 0.2 to about 0.4 micron.

18. A physiologically acceptable emulsion for enhancement of MRI imaging comprising water, a dispersed oil phase selected from the group consisting of an oil and fluorochemical, and mixtures thereof, a surfactant, and a complex of a paramagnetic metal ion and an organic chelator having the formula



wherein from 2 to 5 M groups are hydroxyl, n=0 to 2 and any remaining M group is NR_1R_2, each R_1 is a C_{10}-C_{30} unsaturated aliphatic group and R_2 is hydrogen, hydroxyl or a C_1-C_2 alkyl.

19. The physiologically acceptable emulsion of claim 18 wherein said metal ion is a lanthanide element of atomic numbers 58-70 or a transition metal of atomic numbers 21-29, 42 or 44.

20. The physiologically acceptable emulsion of claim 18 wherein said metal ion is selected from a group consisting Gd(III), Mn(II), iron and dysprosium.

21. The physiologically acceptable emulsion of claim 18 wherein said organic chelator is an acid selected from the group consisting of ethylenediaminetetraacetic acid and diethylenetriaminepentaacetic acid.

22. The physiologically acceptable emulsion of claim 18 wherein said organic chelator is a monoamide or a bisamide of an organic acid selected from a group consisting of diethylenetriaminepentaacetic acid and ethylenediaminetetraacetic acid.

23. The physiologically acceptable emulsion of claim 18 wherein each R_1 is C_{14}-C_{22}.

24. The physiologically acceptable emulsion of claim 18 wherein the organic chelator is a mono or bisamide where R_1 is selected from the group consisting of oleyl, farnesyl, geranyl, erucyl, elaidyl, linoleyl, ricinoleyl, petroselinyl, linolenyl, vaccenyl, linderyl, palmitoleyl, palmitelaidyl, myristoleyl, and myristelaidyl, and where R_2 is selected from the group consisting of methyl, ethyl, and hydroxyl.

25. The physiologically acceptable emulsion of claim 18 wherein said complex is gadolinium diethylenetriaminepentaacetic acid bis(oleylamide).

26. The physiologically acceptable emulsion of claim 18 wherein said chelate complex is gadolinium diethylenetriaminepentaacetic acid mono(oleylamide).

27. The emulsion of claim 18 wherein the fluorochemical is selected from the group consisting of perfluorodecalin, perfluoromethyldecalin, perfluorodimethyladamantane, perfluorooctylbromide, perfluoro-4-methyloctahydroquinolidizine, perfluoro-N-methyl-decahydroquinoline, F-methyl-1-oxadecalin, perfluorobicyclo (5.3.0.) decane, perfluorooctahydroquinolidizine, perfluoro 5,6-dihydro-5-decene, perfluoro-4,5-dihydro-4-octene, perfluorodichlorooctane, perfluorobischlorobutyl ether, and chlorinated perfluorocarbons, and mixtures thereof.

28. The emulsion of claim 18 that is stable after heat sterilization with less than 10 volume % of particles above about 0.8 micron.

29. The emulsion of claim 18 wherein the oil phase contains about 5 to about 25% w/v oil or about 5 to about 55% v/v fluorochemical.

30. The emulsion of claim 18 wherein the oil is selected from the group consisting of mono-, di- and triglycerides, and mixtures thereof.

31. The emulsion of claim 29 wherein the surfactant is present in an amount from about 0.5 to about 10% by weight of the emulsion.

32. The method for MRI imaging of a subject comprising administering to such subject an image-modifying effective amount of the emulsion of claim 1.

33. The method for MRI imaging of a subject comprising administering to such subject an image-modifying effective amount of the emulsion of claim 2.

34. The method for MRI imaging of a subject comprising administering to such subject an image-modifying effective amount of the emulsion of claim 15.

35. The method for MRI imaging of a subject comprising intravenously administering to such subject an image-modifying effective amount of the emulsion of claim 16.

36. The method for MRI imaging of a subject comprising administering to such subject an image-modifying effective amount of the emulsion of claim 18.

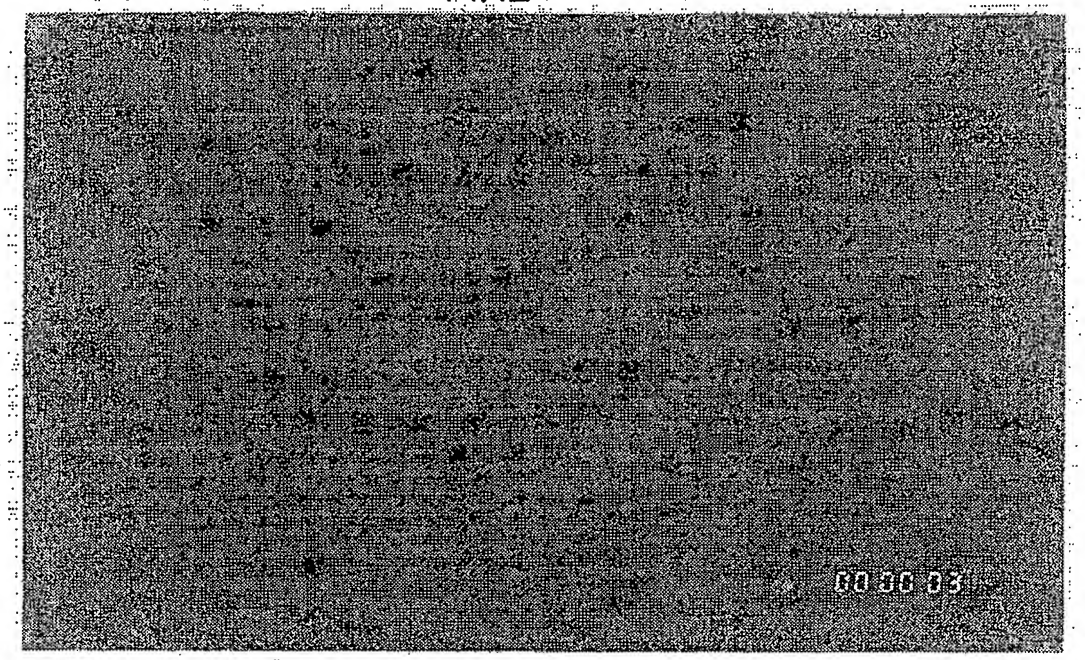
37. The method for MRI imaging of a subject comprising administering to such subject an image-modifying effective amount of the emulsion of claim 24.

38. The method for MRI imaging of a subject comprising administering to such subject an image-modifying effective amount of the emulsion of claim 27.

39. The method for MRI imaging of a subject comprising intravenously administering to such subject an image-modifying effective amount of the emulsion of claim 28.

FIG. 1

FINE



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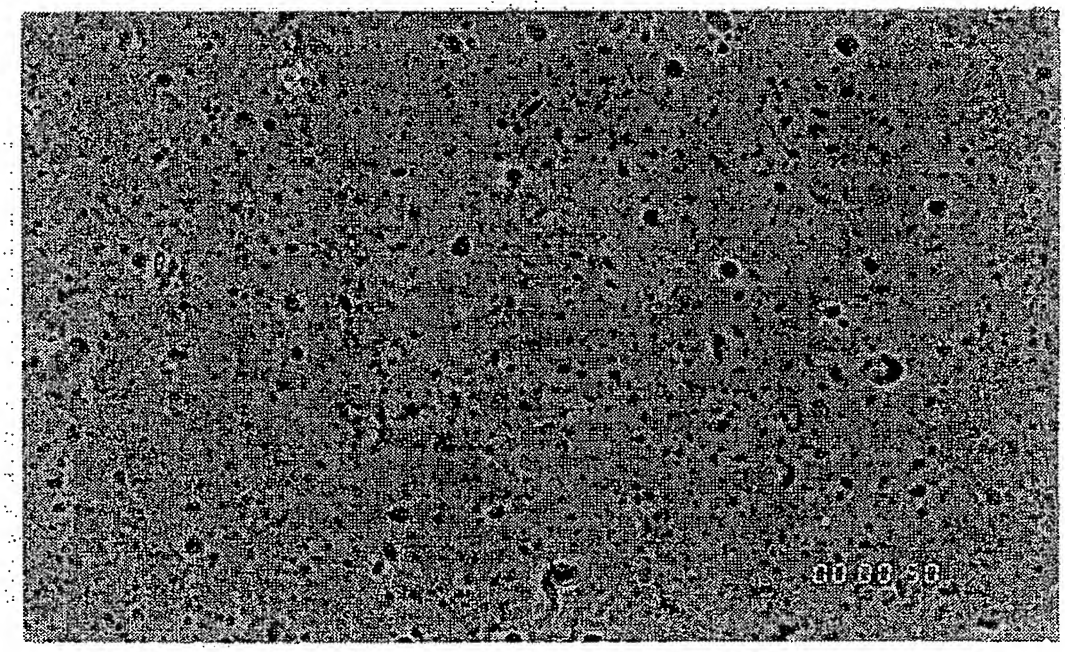
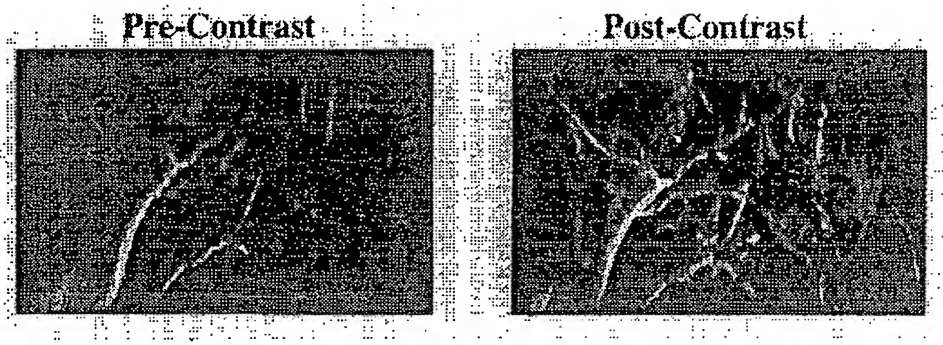


Figure 1. 3D TOF Angiography with GdDTPA-BOA in A) the brain and B) the liver.

A)



B)

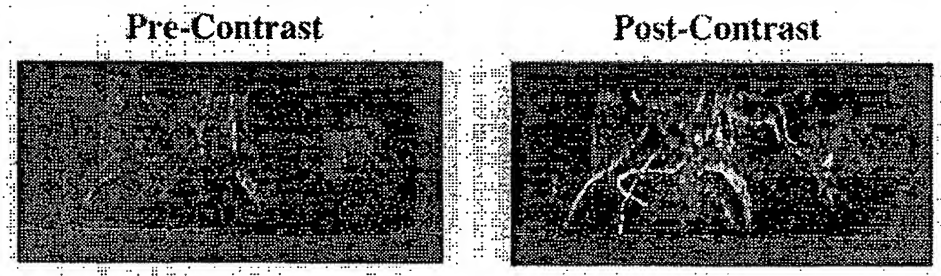
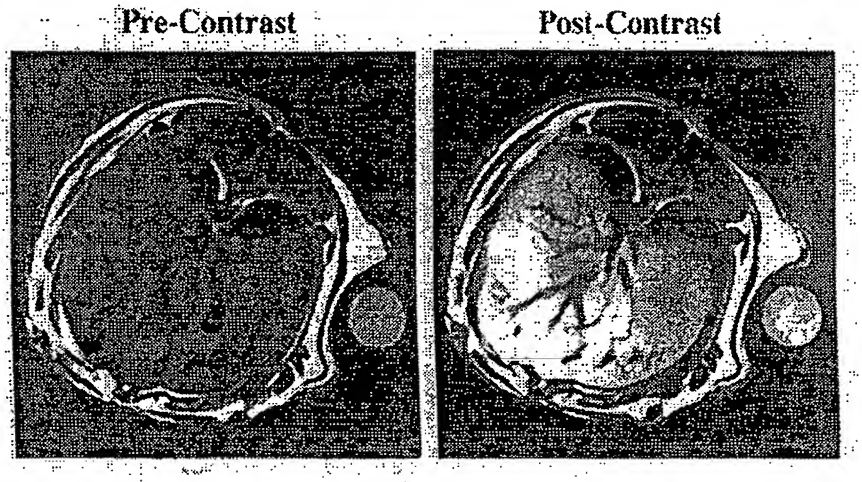


Figure 2. Use of GdDTPA-MOA in the Enhancement of Normal Liver



INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 95/06818

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	MAGN. RESON. MED., 1991, VOL. 19, NO. 2, PAGES 406-15, KABALKA, G. W. ET AL 'Gadolinium-labeled liposomes containing various amphiphilic gadolinium-DTPA derivatives: targeted MRI contrast enhancement agents for the liver' see "Materials and Methods" ---	1-39
X,Y	MAGN. RESON. IMAGING, 1991, VOL. 9, NO. 3, PAGES 373-7, KABALKA, G. W. ET AL 'Gadolinium-labeled liposomes containing amphiphilic Gd-DTPA derivatives of varying chain length: targeted MRI contrast enhancement agents for the liver' see figures see table 1 see page 376, right column - page 377 --- -/--	1-39

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 1995	19.10.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Dullaart, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 95/06818

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	ADV EXP MED BIOL, 1984, VOL. 180, PAGE(S) 835-45, CLARK LC JR ET AL 'Perfluorinated organic liquids and emulsions as biocompatible NMR imaging agents for 19F and dissolved oxygen.' see "CONCLUSION" ---	1-39
Y	WO,A,92 21017 (UNGER EVAN C ;SHEN DEKANG (US)) 26 November 1992 see examples ---	1-39
X,Y	US,A,4 826 673 (DEAN RICHARD T ET AL) 2 May 1989 see examples ---	1-39
X,Y	US,A,4 963 344 (GRIES HEINZ ET AL) 16 October 1990 see examples 2,17,49 ---	1-39
X,Y	US,A,5 120 527 (LI KING CHUEN PETER ET AL) 9 June 1992 cited in the application see the whole document ---	1-39
X,Y	US,A,4 957 939 (GRIES HEINZ ET AL) 18 September 1990 see examples 2,17,49 ---	1-39
P,Y	J MAGN RESON IMAGING, JUL-AUG 1994, VOL. 4, NO. 4, PAGE(S) 631-5, THOMAS SR ET AL 'Evaluation of the influence of the aqueous phase bioconstituent environment on the F-19 T1 of perfluorocarbon blood substitute emulsions.' see abstract see "Materials and Methods" ---	1-39
A	HUM. TOXICOL., 1987, VOL. 6, NO. 6, PAGE(S) 451-458, RAU W. ET AL 'Influence of several chelating agents on the distribution and binding of cadmium in rats' see the whole document -----	1-39

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INTERNATIONAL SEARCH REPORT

Inte. .ional application No.
PCT/US95/06818

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 32-39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (rule 39.1(iv)PCT).

2. [X] Claims Nos.: 1-39
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
please see enclosed sheet ../..

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

INCOMPLETE SEARCH...
1. Obscurities,...
Remark: In view of the large number of compounds, which are defined by the general definition and formulae used in claim(s) 1-39, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application (see guidelines, part. B, chapter III, paragraph 3.6).

INTERNATIONAL SEARCH REPORT

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Inter. nal Application No
PCT/US 95/06818

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